In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 11-118V

(PUBLISHED[1])

EMILY WIRT,	*	
	*	
Petitioner,	*	Filed: April 18, 2014
	*	
v.	*	Special Master
	*	Hamilton-Fieldman
	*	
SECRETARY OF HEALTH AND HUMAN SERVICES ,	*	Vaccine Act Entitlement; Causation-in-fact; Gardasil Vaccination; Rheumatoid Arthritis; Denial.
	*	
Respondent.	*	
	*	

Christina Ciampolillo, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for Petitioner.
Darryl Wishard, United States Department of Justice, Washington, DC, for Respondent.

DECISION

Emily Wirt ("Petitioner") seeks an award under the National Vaccine Injury Compensation Program (hereinafter "the Program"[2]). Petitioner received a third dose of the quadrivalent human papillomavirus vaccination ("HPV" or "Gardasil") on March 4, 2008, which she alleges caused the injury of rheumatoid arthritis ("RA"), from which she now suffers. Petition ("Pet.") at 1. For the reasons set forth below, the undersigned concludes that Petitioner is not entitled to an award.

[1] Because this Published Decision contains an explanation for the undersigned's action in this case, she intends to post this document on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). Therefore, as provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party (1) that is trade secret or commercial or financial information and is privileged or confidential, or (2) that are medical files and similar files the disclosure of which would constitute a clearly unwarranted invasion of privacy." Otherwise, this entire document will be available to the public. *Id.*

[2] The applicable statutory provisions defining the Program are found at 42 U.S.C. § 300aa-10 *et seq.* (2006 ed.).

I

PROCEDURAL HISTORY AND FACTUAL HISTORY

A. Procedural History

On February 25, 2011, Petitioner filed a petition for compensation under the National Childhood Vaccine Injury Act of 1986. The petition alleged that as a result of receiving the third administration of the HPV vaccination on March 4, 2008, Petitioner suffered a rheumatologic injury. Pet. at 1. Respondent filed a Rule 4(c) Report on May 23, 2011, which stated that Petitioner had insufficient evidence under all three prongs of *Althen* to satisfy the burden of proof necessary for vaccine compensation. *See* Resp't's Rep. at 12, ECF No. 11.[3]

On March 29, 2012, Petitioner filed the expert report of Dr. Kristin M. Gowin, M.D., with referenced medical literature attached as Exhibit 18, Tabs A through J, and Dr. Gowin's curriculum vitae ("CV"). Filing, ECF No. 23. On June 8, 2012, Respondent filed the expert report of Dr. Robert W. Lightfoot, Jr., M.D., in conjunction with his CV and medical literature, labeled Exhibits A through E. Filing, ECF No. 26.

Petitioner filed a Supplemental Expert Report from Dr. Gowin, as a response to the expert report of Dr. Lightfoot, on October 12, 2012. Filing, ECF No. 30.

On March 4, 2013, the case was reassigned to the undersigned pursuant to Vaccine Rule 3(d). Order, ECF No. 31. Over the next month, medical records and literature were filed. On April 4, 2013, Petitioner noted that all medical records had been filed. Pet'r's Status Rep., ECF No. 40. On April 21, 2013, the undersigned filed two exhibits, Court Exhibit 1 and Court Exhibit 2, along with a pre-hearing order, indicating some of the pertinent issues the undersigned wished to discuss at hearing. Order and Court Exhibits, ECF No. 41.

An evidentiary hearing was held in Washington, DC on April 23, 2013. *See* Transcript of Proceedings ("Tr."), ECF No. 44. The parties filed simultaneous post-hearing briefs on June 12, 2013. Filings, ECF Nos. 47, 48. The matter is now ripe for a decision on entitlement.

B. Gardasil Vaccine and Alleged Injury, Rheumatoid Arthritis

1. Gardasil

Gardasil is a relatively new vaccine. Gardasil Package Insert at 1, *available at* http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf. It was developed to immunize young women (although it is also given to young men) against the human papillomavirus. *Id.* Gardasil is a recombinant vaccine, not a live virus vaccine. *Id.* That is, Gardasil "[i]s a non-infectious recombinant quadrivalent vaccine prepared from the purified virus-like particles (VLPs) of fermentations in recombinant *Saccharomyces cerevisiae* and self-assembled into VLPs." *Id.* at 13. There are at least 130 genetically different HPV subtypes

[3] *See Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274 (Fed. Cir. 2005).

known to date. *See* Court Exhibit 1 at 1, ECF No. 41.[4] Two of them, HPV 16 and HPV 18, are known to cause cervical, esophageal, and anal cancer, and two, HPV 6 and HPV 11, are known to cause genital warts and herpes. *Id.* at 1-2. These four subtypes are incorporated into the quadrivalent Gardasil vaccine. *See* Gardasil Package Insert at 1.

2. Rheumatoid Arthritis

Rheumatoid Arthritis is "a chronic systemic disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures and by muscle atrophy and rarefaction of the bones." *See* Dorland's Illustrated Medical Dictionary 157 (32nd ed. 2012). While RA can affect large joints such as hips and shoulders, that manifestation of the disease generally occurs late in the course of the disease. Tr. at 36-37, 154-59. The causes of RA are unknown. *Id. See also* Tr. at 35, 117-18. However, it is known that RA is an autoimmune disease. One significant diagnostic marker for RA is an elevated level of anti-cyclic citrullinated peptide ("anti-CCP") antibodies in the blood of the patient. Tr. at 118-21; *see also* Pet'r's Ex. 18, Tab F at 1.[5]

C. Facts

Emily Wirt was born on April 9, 1986. Pet'r's Ex. 2 at 2.

Her relevant medical history begins on December 26, 2006, when Dr. Daniel Kambic, M.D., noted that Petitioner had a small cystic lesion on the base of her right elbow and experienced dislocation of her left hip. Pet'r's Ex. 3 at 3. On December 28, 2006, Dr. Damico, D.O., referred Petitioner to Dr. Bahia, M.D. Pet'r's Ex. 4 at 4. Dr. Bahia noted that Petitioner had a history of chronic hip pain bilaterally for two years and further noted to "[r]ule out arthritis." *Id.*

On January 23, 2007, Petitioner was treated by Dr. O'Neill, a physiatrist, for bilateral hip pain. Pet'r's Ex. 4 at 14-15. Dr. O'Neill noted that Petitioner was a former ballet dancer who had constant aches and pains laterally in both hips, and on physical examination, her femurs were "internally rotated bilaterally despite her foot position being straight indicating some tibial torsion." *Id.* at 14. The impression was dynamic instability of bilateral hips with excess internal rotation and pain. *Id.* The recommendation was physical therapy ("PT") to increase strength of hip stabilizers. *Id.* at 15.

Dr. O'Neill saw Petitioner again on April 17, 2007, to check her PT program; Dr. O'Neill determined that additional PT was needed. Pet'r's Ex. 4 at 20. Petitioner was treated at the Student Health Center at St. Joseph's University ("SJU"), where she was a student, on July 11, 2007, for fatigue, muscle aches, and a sharp pain in the back of her head. Pet'r's Ex. 5 at 5. She noted that these complaints had started in June 2007, and were intermittent; the recommendation was to follow up with her family doctor. *Id*.

[4] Margaret Stanley, Immunobiology of HPV and HPV vaccines, 109 Gynecologic Oncology. S15 (2008).

[5] J. Shi, et al., Prevalence and significance of antibodies to citrullinated human papilloma virus-47 E2345-362 in rheumatoid arthritis, 31 Journal of Autoimmunity. 131 (2008).

Dr. Grotzinger saw Petitioner on July 13, 2007, for an annual check-up; Petitioner received the first of three doses of the Gardasil vaccine at that appointment. Pet'r's Ex. 11 at 2.

Petitioner was seen by Nurse Practitioner Anna Kambic on July 16, 2007, for fatigue, a sore throat, and an intermittent headache since the beginning of June 2007; the headache was at the base of the neck and "develops as the day goes on." Pet'r's Ex. 3 at 1. The physical examination noted trapezius muscle spasm bilaterally, and the diagnoses were tension headache and allergic rhinitis. *Id.* Her labs taken that day included a complete blood count ("CBC"), a thyroid function test, and a basic metabolic panel, all of which were normal. *Id.* at 10.

Dr. O'Neill saw Petitioner on July 25, 2007, for an assessment of her PT progress. Petitioner reported that the program was very helpful, and Dr. O'Neill noted that Petitioner was under a lot of stress. Pet'r's Ex. 4 at 25.

A second dose of the HPV vaccine was given in Petitioner's left deltoid on October 15, 2007, at Dr. Grotzinger's office. Pet'r's Ex. 2 at 13. She also received an influenza vaccine in the left deltoid on October 19, 2007, at the Student Health Center at SJU. Pet'r's Ex. 5 at 5.

Petitioner received a third dose of the HPV vaccine in her left deltoid at Dr. Grotzinger's office on March 4, 2008. Pet'r's Ex. 2 at 15. In her affidavit, Petitioner averred that later that month, following the March 4 vaccine administration, "[she] began to experience pain in [her] shoulders." Pet'r's Ex. 15 at 1. Petitioner also reported in her affidavit that she had swelling and stiffness in her hands and feet in June of 2008. *Id.* at 2. There is no medical record of these complaints, however, until Petitioner's visit to Dr. Hillman on July 30, 2008. Pet'r's Ex. 14 at 3. The records of that visit indicate that Petitioner reported that she could not carry a laptop due to ongoing shoulder pain. *Id.* at 1-3. However, she did not raise the swelling and stiffness in her hands and feet in her visit with Dr. Hillman. *See generally* Pet'r's Ex. 14.

On August 12, 2008, Petitioner presented to Dr. Papp-Mlodzienski, D.P.M., for a complaint of chronic pain in the ball of the foot. Pet'r's Ex. 17 at 1. On examination, Dr. Papp-Mlodzienski noted that "pedis and posterior tibial pulses are normal, graded at 2/4 bilateral. Capillary filling time with the leg elevated is <5 seconds at the level of the digital tufts bilaterally." *Id.* Petitioner was also noted to have "[e]picritic sensation including sharp-dull, light touch, proprioception. Mulder's sign was not observed in either foot." *Id.* Dr. Papp-Mlodzienski's impression was "Raynoud's Phenomenon. Metatarsalgia. Capsulitis." *Id.*

Petitioner saw Dr. Chou, an orthopedist, for bilateral hip pain, weakness in the shoulders with a sense of instability, and stiffness in her hands and feet, especially in the morning, on September 23, 2008. Pet'r's Ex. 9 at 2. After a review of foot x-rays and lab tests, which were normal, the impressions were bilateral external snapping hip syndrome, a shoulder condition of Atraumatic Multidirectional Bilateral Responding to Rehabilitation and Rarely Requiring Inferior capsule shift syndrome ("AMBRI"), and significant morning stiffness with an unknown etiology. Pet'r's Ex. 9 at 4. That same day, Petitioner also saw Dr. Papp-Mlodzienski, again for chronic pain in the ball of the foot. Pet'r's Ex. 12 at 1. The impression was Raynoud's phenomenon, metatarsalgia, capsulitis, and pes valgus. *Id.* The left foot x-ray was normal. *Id.* at 2. Petitioner was treated with arch supports, orthotics for her shoes, and PT. *Id.* at 1.

Petitioner saw Dr. Whalen, a rheumatologist, on November 10, 2008, for stiffness and pain in her body since June 2008. Pet'r's Ex. 10 at 1. Petitioner was noted to have been experiencing pain in her hands, feet, knees, shoulders, neck, left temporomandibular joint ("TMJ"), and left wrist. *Id.* Petitioner was noted to have a problem with sleeping through the night, and she did not awaken feeling rested. *Id.* Lab tests obtained at that visit included negative/normal tests for anti-CCP antibody, antinuclear antibody ("ANA"), C3, C4, total complement, and tests for anti-phospholipid syndrome. *Id.* at 9. Petitioner's rheumatoid factor ("RF") level was elevated at 118 (normal: 0-29), and ESR and CRP, two very non-specific tests for inflammation in the body, were elevated at 75 mm/hr and 38.4 mg/dl respectively. *Id.* at 8-9. Dr. Whalen did not comment on these abnormalities in subsequent notes. *Id.* Dr. Whalen's impression was fibromyalgia, myofascial pain, and chronic sleep disorder; Petitioner's treatment was to start a trial of Medrol (an oral glucocorticosteroid) with Dose pack and Flexeril (a muscle relaxant). *Id.* at 2.

Dr. Whalen had a follow up visit with Petitioner on December 8, 2008, where Petitioner reported that she was still not sleeping well but the Medrol was helping. *Id.* at 4. At this time, there was no noted change in diagnosis, and Petitioner's Medrol regimen was continued. *Id.* at 5.

Dr. Epstein, M.D., a rheumatologist at Pennsylvania Hospital in Philadelphia, saw Petitioner emergently on January 20, 2009. Pet'r's Ex. 8 at 9-10. Petitioner reported a history of stiffness in her hands and feet since June 2008. *Id.* at 8. She had been seen by a podiatrist and rheumatologist, but she reported that no diagnoses were made. *Id.* She also complained of occipital headaches. *Id.* The physical exam showed tenderness in the small joints of both hands and both wrists, which also included decreased range of motion; it was also noted that Petitioner had painful shoulder motion bilaterally and tender ankles. *Id.* Additionally, the metatarsal phalangeal ("MTP") joints were tender and slightly swollen. *Id.* The lab studies were RF positive, ANA negative, ESR 75 elevated, and HLA-B27 negative. Pet'r's Ex. 8 at 19, 23. Petitioner's labs also showed that her anti-CCP antibody count was 34. Pet'r's Ex. 8 at 22. The lab results noted the reference range for anti-CCP antibody: a count that was greater than or equal to 20 units indicated a positive detection. *Id.* at 23. Dr. Epstein's impression was sero-positive RA and probable fibromyalgia. Pet'r's Ex. 8 at 10. Dr. Epstein's recommendation was to consider starting a disease-modifying medication. *Id.*

From July 12, 2009 until March 2010, Petitioner went to an acupuncture practice for RA pain, shoulder pain, and neck pain. Pet'r's Ex. 7 at 7-14. On August 13, 2009, Petitioner was seen in a follow up appointment with Dr. Epstein, who noted that Petitioner was unable to tolerate "Methotrexate and Arava," and had elected to initiate therapy with Simponi. Pet'r's Ex. 8 at 4. On January 17, 2010, Petitioner received the H1N1 flu vaccination. Pet'r's Ex. 13 at 5. Petitioner's colposcopy lab results from October 22, 2010, noted a post-operative diagnosis of "Pap history of Low grade squamous intraepithelial lesion." Pet'r's Ex. 13 at 102. These results also revealed a final diagnosis of "[f]eatures suggestive of human papillomavirus (HPV) infection and mild chronic cervicitis." Pet'r's Ex. 13 at 103. There is no record of Petitioner having been tested for HPV infection prior to October 22, 2010.

II

SUMMARY OF EXPERT WITNESSES' CREDENTIALS

A. Petitioner's expert- Dr. Kristin M. Gowin, M.D.

Dr. Kristin M. Gowin attended Miami University in Oxford, Ohio, and received a Bachelor of Arts Degree in Zoology in 1986. Pet'r's Ex. 19 at 1. She graduated from the University of Cincinnati College of Medicine with a degree in medicine in 1990, and completed her residency in internal medicine at the Milton S. Hershey Medical Center from 1990 to 1993. *Id.* at 1-2. Dr. Gowin attended the University of Pennsylvania School of Medicine and received a Master of Science in Clinical Epidemiology ("MSCE") in June of 2002. *Id.* at 1. She served as a Faculty Fellow at the University of Pennsylvania School of Medicine, Center for Clinical Epidemiology and Biostatistics, from 1997 to 1999, and was additionally a Fellow in the Division of Rheumatology from 1994 to 1998. *Id.*

Dr. Gowin was appointed as Instructor in Medicine at the Milton S. Hershey Medical Center from 1993 to 1994, served as an attending physician in rheumatology at the Philadelphia Veterans Affairs Medical Center from 1997 to 1999, and also served as an instructor in the division of rheumatology at the Hospital of the University of Pennsylvania from 1998 to 1999. *Id.* at 2.

Dr. Gowin has received the American College of Rheumatology/ Pharmacia Upjohn Physician Scientist Development Award and the MacKracken Award from the Arthritis Foundation. *Id*. She belongs to the American College of Rheumatology, the Buncombe County Medical Society, the North Carolina Medical Society, the Arthritis Foundation, the Psoriasis Foundation, and the North Carolina Rheumatology Association. *Id.* She is licensed to practice medicine in North Carolina. *Id.* Dr. Gowin has 16 publications/presentations listed on her CV. *Id.* at 3-4. Dr. Gowin is not an immunologist.

B. Respondent's expert- Dr. Robert W. Lightfoot, M.D.

Dr. Robert W. Lightfoot attended Vanderbilt University where he graduated *Phi Beta Kappa* with a Bachelor of Arts Degree in 1958, and Vanderbilt University School of Medicine, where he graduated with a degree in medicine in 1961. Resp't's Ex. B at 1. Dr. Lightfoot interned at the Columbia Presbyterian Medical Center from July 1, 1961 to June 30, 1962, completed a residency at the same institution from July 1, 1962 to June 30, 1963, and an additional year of residency at Vanderbilt University Hospital from July 1, 1963 to June 30, 1964. *Id.* He completed his fellowship in rheumatology at Columbia University from July 1, 1964 to June 30, 1966. *Id.*

Dr. Lightfoot served in the US Army Medical Corps from August 1, 1966 to July 31, 1968. Resp't's Ex. B at 1. Dr. Lightfoot also served as Chief of the Rheumatology Division at the Medical College of Wisconsin from July 1, 1976 to September 30, 1986. *Id.* Dr. Lightfoot has also served as an Associate Professor of Medicine and a Professor of Medicine at the Medical College of Wisconsin, as the Division Director of the Allergy, Immunology, and

Rheumatology Division at the University of Kentucky at Lexington, and as a Professor of Medicine and a Professor of Medicine Emeritus at the University of Kentucky, College of Medicine. *Id.* at 2.

Dr. Lightfoot is board certified by the American Board of Internal Medicine and the American Board of Internal Medicine in Rheumatology. *Id.* at 1. He is currently licensed in Kentucky. *Id.* Dr. Lightfoot is a member of the American College of Rheumatology and has co-authored 41 peer-reviewed articles, which are listed on his CV. *Id.* at 3, 14-18. Dr. Lightfoot is also not an immunologist. However, Dr. Lightfoot does have some training and experience in immunology. Tr. at 108-14.

III

ISSUE TO BE DECIDED

Petitioner seeks a Program award, contending that her RA was "caused-in-fact" by an HPV vaccination administered on March 4, 2008. After careful consideration, the undersigned concludes that Petitioner has failed to demonstrate causation.

Petitioner's theory of the case may be briefly summarized as follows: Petitioner's expert contends that Petitioner's receipt of the third dose of the HPV vaccination caused Petitioner's RA because there is both biologic plausibility and temporal support contained within the medical literature and records. First, Petitioner's expert supports her contention with the assertion that immunologic changes in patients who will eventually develop RA can be seen several years prior to the onset of symptoms given the appropriate trigger to the immune system. Pet'r's Ex. 18 at 4. Petitioner contends that the HPV vaccination acted as a trigger, causing an onset or flare of RA in Petitioner, by activating antigen-dependent T lymphocytes. *Id.* Petitioner's expert states, "[t]he activation of the immune cascade causes ingrown [sic] of blood vessels, recruitment of further immune cells (that produce antibodies like the classic rheumatoid factor and anti CCP [sic]) and proliferation of the lining of the joint (synovium) that eventually causes damage to the cartilage." *Id.*

Petitioner's expert also argues that there is temporal support for a finding of vaccine causation because "[t]he onset of her disease [Petitioner's RA] was several weeks after the HPV vaccination series, which is consistent with reactive autoimmune syndromes reported in the medical literature." *Id.* Petitioner's position is that since the production of auto-antibodies takes time, and repeated exposure to an antigen is necessary to trigger illness, the passage of several weeks between receipt of the third dose of vaccine and satisfaction of the diagnostic criteria for RA is temporally reasonable. *Id.*

Respondent disagrees with Petitioner's arguments. Respondent contends that the time of onset of Petitioner's RA disease remains unclear from the medical records, as Petitioner experienced hip and shoulder pain, had an elbow nodule, and experienced fatigue/fever complaints antedating vaccination. Resp't's Ex. A at 8. Additionally, Petitioner did not test positive for RF until November of 2008, eight months after vaccination. Pet'r's Ex. 10 at 9. Respondent argues that it is almost impossible to say when RA emerged as a cause of

Petitioner's pain. Resp't's Ex. A at 8. Respondent also argues that Petitioner's expert report failed to identify a biologically plausible theory causally connecting vaccination to injury, other than to cite epidemiological studies and anecdotal case reports, which have limited reliability. *Id.* Furthermore, Respondent argued that Petitioner's expert failed to indicate why the vaccine would be more likely to cause an autoimmune disorder than the persistent, ongoing natural HPV infection, with which Petitioner was diagnosed in 2010. *Id.*

After carefully considering all of the evidence in the record, the undersigned must *reject* Petitioner's claim that her RA was caused by the HPV vaccination that she received on March 4, 2008. The undersigned will outline below why Petitioner has failed to demonstrate that it is "more probable than not" that her condition was caused by this vaccination.

IV

APPLICABLE LEGAL STANDARD

To receive compensation under the Program, the petitioner must prove either: (1) that the petitioner suffered a "Table Injury" -- i.e., an injury falling within the Vaccine Injury Table -- corresponding to one of her vaccinations, or (2) that the petitioner suffered an injury that was actually caused by her vaccination. *See* 42 U.S.C. §§ 300aa-13(a)(1)(A) and 300aa-11(c)(1). Petitioner in this case is asserting a non-Table vaccine injury claim.

To establish causation-in-fact in a non-Table case, the petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. The petitioner is required to prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010) (quoting *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Secretary of Health and Human Services*, the Federal Circuit Court of Appeals set forth a three-pronged test used to determine whether a petitioner has established the causal link between the administered vaccine and the claimed injury. *See Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). The *Althen* test requires the petitioner to set forth: "[a] medical theory causally connecting the vaccination and the injury, a logical sequence of cause and effect showing that the vaccination was the reason for the injury, and a proximate temporal relationship between vaccination and injury." *Id.* To establish causation by a preponderance of the evidence, a petitioner is required to satisfy each of the three prongs of *Althen*.

Under the first prong of *Althen*, a petitioner must demonstrate the biological plausibility of her theory by proffering a scientific pathogenesis underlying the alleged causal relationship. The petitioner must answer affirmatively the question "[**c]an** the vaccine(s) cause the injury alleged?" *See Pafford v. Sec'y of Health & Human Servs*., No. 01-0165V, 2004 WL 1717359, at *9 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (Fed. Cl. 2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006) (emphasis added). This may be accomplished in a number of ways. For

example, reliability and plausibility of pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory, so as to render it credible. *See Pafford*, 2004 WL 1717359, at *4; s*ee also Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877, at *21 (Fed. Cl. Spec. Mstr. May 30, 2013). Epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of plausibility; articles published in respected medical journals, which have been subjected to peer review, are also persuasive. *Id. See also Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision oftentimes is based on the credibility of the experts and the relative persuasiveness of their competing theories."); *Terran v. Sec'y of Health & Human Servs.,* 195 F.3d 1302, 1316 (Fed. Cir. 1999), *citing Daubert v. Merrell Dow Pharmaceutical, Inc.*, 509 U.S 579 (1993). However, publication "does not necessarily correlate with reliability," because "in some instances well-grounded but innovative theories will not have been published." *Daubert*, 509 U.S. at 593.

A petitioner must prove that the vaccine actually **did** cause "the injuries or symptoms that manifested in this case" to satisfy the second prong of *Althen*. *See Pafford*, 2004 WL 1717359, at *4; *see also Althen*, 418 F.3d at 1278 (petitioner must establish a "logical sequence of cause and effect showing that the vaccination was the reason for the injury."). Again, the petitioner's burden of proof is by a preponderance of the evidence. *Pafford*, 2004 WL 1717359, at *4. A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury. *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). Rather, a petitioner must explain how and why the injury occurred. *Pafford*, 2004 WL 1717359, at *4; *Strother v. Sec'y of Health & Human Servs.*, 21 Cl. Ct. 365, 370 (Fed. Cl. Aug. 14, 1990), *aff'd*, 950 F.2d 731 (Fed. Cir. 1991). Ruling out other potential causes is an important element but does not itself establish causation. *Pafford*, 2004 WL 1717359, at *4. Additionally, mere conjecture or speculation does not meet the preponderance standard. *Id. Snowbank Enterprises v. United States*, 6 Cl. Ct. 476, 486 (Fed. Cl. Oct. 26, 1984).

Under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen* 418 F.3d at 1278. The Court cannot infer causation from temporal proximity alone, however. Where a petitioner's expert viewed the temporal relationship as the "key" indicator of causation, the claim failed. *See Grant*, 956 F.2d at 1148 ("When a petitioner relies upon proof of causation in fact . . . , a proximate temporal association alone does not suffice to show a causal link between the vaccination and the injury."); *see also Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983) (stating that inoculation is not the cause of every event that occurs within a ten day period following it).

A petitioner who demonstrates by a preponderance of the evidence that she suffered an injury caused by vaccination is entitled to compensation, unless the respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994).

V

ANALYSIS

A. Althen Prong One - A Plausible Medical Theory

Under the first prong of *Althen*, Petitioner is required to set forth a medical theory, explaining how the HPV vaccination can cause RA. *Althen*, 418 F.3d at 1278. The proffered "reputable" explanation must be scientifically "sound" and "reliable." *See Moberly*, 592 F.3d at 1325; *Althen*, 418 F.3d at 1278; *see also Knudsen*, 35 F.3d at 548 (Fed. Cir. 1994) (a causation theory before a special master must be supported by a "sound and reliable" medical or scientific explanation). Furthermore, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26.

Courts have issued a number of decisions discussing what constitutes a "reputable medical or scientific explanation" of a theory sufficient to satisfy the aforementioned requirement. *Id.* at 1323. For example, a petitioner who provides a theory that the government concedes is plausible will satisfy *Althen's* first prong. *See Jay v. Sec'y of Health & Human Servs.*, 998 F.2d 979, 984 (Fed. Cir. 1993) (a reputable and uncontradicted medical explanation connecting facts to an on-Table injury demonstrates causation as a matter of law). A theory that has basic indicia of reliability that is put forward by qualified experts will also satisfy the first prong of *Althen. See Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006) ("the first prong of the *Althen* . . . test was satisfied by the finding that the hepatitis B vaccine can cause [rheumatoid arthritis].").

By contrast, "where basic indicia of reliability do not exist, the special master may reject a petitioner's medical theory." *Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 470 (Fed. Cl. Apr. 18, 2012) (discussing generally that where basic indicia of reliability does not exist regarding a petitioner's medical theory, the special master may reject that theory); *Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1253-54; *Moberly*, 592 F.3d at 1322. Thus, a special master's conclusion that a theory relying upon "a literature review based on two papers from the early 1950s, which in turn considered vaccine cases between 1929 and 1952" was insufficient to satisfy *Althen's* first prong was affirmed. *Broekelschen*, 618 F.3d at 1350. A theory linking a pertussis vaccine to brain damage was also rejected by a special master when the theory had never been tested and was criticized by the government's expert as biologically implausible. *Moberly*, 592 F.3d at 1325 (testimony of petitioner's expert was "contradictory and confusing" and "shockingly poor"). *Id.* at 1321. Similarly, the Federal Circuit has approved of a special master's rejection of medical literature that had no relation to the question of causation. *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1349 (Fed. Cir. 2010); *see also Porter*, 663 F.3d at 1252.

In this case, the theory in dispute is Petitioner's assertion that the HPV vaccination *can* cause the autoimmune disorder of RA. Petitioner's theory, put forth through the testimony of Dr. Gowin, is premised on two scientific concepts: molecular mimicry; and the argument set forth in an article by Shi, et al., that a protein sequence present in one variant of HPV, HPV-47, when

citrullinated,[6] may play a role "in the induction of disease-specific antibodies in RA." Pet'r's Ex. 18, Tab F at 6.[7]

For the theory of molecular mimicry to work, there has to be a known or suspected molecular cause of the disease for the vaccine molecule to mimic. One basic theory of the development of an autoimmune disease such as RA involves the introduction of a foreign molecule, an antigen, to which the body's immune system responds by, among other things, creating antibodies directed at the antigen. At some point, the immune system begins to recognize "self" molecules that have enough amino acid sequence and structural similarities to the antigen to "mimic" the antigen and prompt a similar antibody response. Tr. at 12-13.

Beginning from the premise that anti-citrullinated profilaggrin peptide antibodies "have been shown to play important roles in the pathogenesis of RA," (Pet'r's Ex. 18, Tab F at 1[8]), the authors of the Shi study set out to determine whether a viral protein sequence homologous to the critical protein sequence in citrullinated profilaggrin exists, and, if so, whether a citrullinated version of that viral protein sequence would engender a similar RA reactive response to that engendered by citrullinated profilaggrin. Using the National Center for Biotechnology Information (NCBI) version of the Basic Local Alignment Search Tool (BLAST), the researchers identified the HPV-47 sequence $E2_{345\text{-}362}$ as "the highest homologous viral sequence to $profilaggrin_{306\text{-}324}$," (Pet'r's Ex. 18, Tab F, at 1[9]), and synthesized a citrullinated version of that viral protein sequence for use in their study. *See* Pet'r's Ex. 18, Tab F at 1.[10] They then exposed the sera of patients with RA, patients with other autoimmune diseases, and healthy controls, to the citrullinated HPV-47 protein sequence, as well as to the HPV-47 protein sequence that had not been citrullinated. They found a significantly higher reactivity to the citrullinated $E2_{345\text{-}362}$ in the RA patients than in any of the control groups. However, they found no such reaction to the $E2_{345\text{-}362}$ protein sequence that had not been citrullinated. Pet'r's Ex. 18, Tab F at 3.[11]

Neither Dr. Gowin's report nor her testimony was altogether clear in setting forth her theory of causation. However, Dr. Gowin's causal theory appears to be that the HPV vaccine, "modified" with citrullination, "mimics" the citrullinated profilaggrin protein sequence in the same way that citrullinated HPV-47 $E2_{345\text{-}362}$ protein sequence mimicked citrullinated

[6] Citrullination is the conversion of arginine in a protein sequence to the amino acid citrulline. *See* Dorland's Illustrated Medical Dictionary 366 (32nd ed. 2012); Tr. at 40-58.

[7] *See* J. Shi, et al., at 135.

[8] *See* J. Shi, et al., at 131.

[9] *See* J. Shi, et al., at 131.

[10] "The first arginine residue (R348) located between threonine and glycine in $E2_{345\text{-}362}$ was substituted by citrulline." J. Shi, et al., at 131.

[11] J. Shi, et al., at 133.

profilaggrin in the Shi study. HPV-47 however is not one of the HPV subtypes included in the Gardasil vaccine. Unfortunately, there is no evidence in the record, nor could Dr. Gowin provide any when questioned, that any of the HPV subtypes that are included in the vaccine has a protein sequence similar to that found by the Shi researchers in HPV-47, HPV-47 $E2_{345-362}$. Tr. at 55-56. That protein sequence is one of the linchpins of the Shi study. Pet'r's Ex. 18, Tab F.[12] If the protein sequence is not present, the molecular mimicry of the profilaggrin protein sequence and the RA response it allegedly engenders, would not occur. Thus, evidence that the sequence is present in at least one of the four HPV subtypes in the vaccine would have been necessary to a finding that this theory is at all plausible. *See Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (Fed. Cl. 2011), *aff'd*, 463 Fed. App'x 932 (Fed. Cir. 2012) ("A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered."); *see also Cedillo*, 617 F.3d at 1339 (quoting *General Electric Co. v. Joiner*, 522 U.S. 136, 146 (1997)).

Even if one assumes, for sake of argument, that the protein sequence is present in the natural variant of one or more of the HPV subtypes included in the vaccine, the protein sequence may not survive the recombinant vaccine formulation process intact to be included in the vaccine. Whether the protein sequence at issue here, even if present somewhere in the genetic sequence of the live virus, exists on the major capsid protein portion of the virus types, and if so, whether it would survive the purification, fermentation, and self-assembly processes of recombinant vaccine production, are questions not answered at hearing or by any information in the record.

Finally, there is the question of citrullination. Citrullination is the second linchpin of the Shi study. The Shi study noted "significantly higher" RA antibody reactivity to citrullinated HPV-47 $E2_{345-362}$; however, there was "no statistical difference" in reactivity to $E2_{345-362}$ that had not been citrullinated. Pet'r's Ex. 18, Tab F at 3.[13] Thus, not just the protein sequence, but the citrullinated protein sequence, is essential. In her conclusions, Dr. Gowin references "vaccine modified with citrullination" as an antigen for Petitioner's RA. Pet'r's Ex. 18 at 3. However, she provides no basis for her conclusion that the HPV proteins in the vaccine either can be or have somehow been modified to include a citrullinated protein sequence. Again, without some evidence of the existence of the protein sequence in citrullinated form, the biologic plausibility of Petitioner's theory fails.

Petitioner's expert report and medical literature thus leave the following unanswered questions: Do anti-CCP antibodies cause or simply predict the existence of the disease RA? If the antibodies do cause RA, would a viral protein sequence that is partially homologous to the citrullinated profilaggrin sequence to which the antibodies react have the same causative effect? Do genotypes of HPV that comprise the Gardasil vaccine include such a homologous protein sequence? If the virus types in the vaccine do include such a protein sequence, would the sequence survive the recombinant vaccine formulation process intact? And if the protein sequence particles did actually exist and survive to this stage in the process, would citrullination of that viral protein sequence occur, and if so, how would that process occur? There are simply

[12] J. Shi, et al., at 131-35.

[13] J. Shi, et al., at 133.

too many unknowns, too many gaps in the analytical process of the theory, to allow the undersigned to conclude that Petitioner has proven "a medical theory causally connecting the vaccination and the injury." *Althen*, 418 F.3d at 1278; *see Joiner*, 522 U.S. at 146 ("[t]here is simply too great an analytical gap between the data and the opinion proffered."). Petitioner has therefore not met her burden under the first prong of *Althen*.

Dr. Gowin also attempts to establish theoretical causation in this case by citing studies by Block and Slade (Pet'r's Ex. 18, Tab C; Pet'r's 18, Tab D)[14] purporting to show a temporal connection between HPV vaccine administration and VAERS reports of RA occurrence.[15] The reliability of VAERS data has often been called into question under the Vaccine Program. *See Capizzano v. Sec'y of Health & Human Servs.*, 63 Fed. Cl. 227, 231 (Fed. Cl. Dec. 7, 2004) (discussing that VAERS data has limited value due to the manner in which it is collected, the lack of confirmation of the reported information, and the lack of any systemic analysis); *Manville v. Sec'y of Health & Human Servs.*, 63 Fed. Cl. 482, 494 (Fed. Cl. Nov. 24, 2004) (VAERS reports can be filed by anyone, thus raising questions about the quantity and quality of the information gathered); *Ryman v. Sec'y of Health & Human Servs.*, 65 Fed. Cl. 35, 39-43 (Fed. Cl. Apr. 8, 2005) (VAERS reports may be biased toward pre-existing notions of adverse events); *Analla v. Sec'y of Health & Human Servs.*, 70 Fed. Cl. 552, 558 (Fed. Cl. Mar. 8, 2006) (discussing "concerns about the reliability of VAERS data."). As stated in the Slade study, "VAERS data must be interpreted cautiously and cannot generally be used to infer causal associations between vaccines and [an adverse event following immunization]." Pet'r's Ex. 18, Tab D at 8-9.[16] VAERS data alone, without the opinion of a medical expert and/or medical records showing a causal connection between vaccination and injury, is not proof of a causal connection. As discussed above, Dr. Gowin's expert opinion is not sufficient to establish causation; the VAERS data therefore stands alone, and is insufficient to meet Petitioner's burden of proof concerning causation.

[14]Stan L. Block, et al., Clinical Trials and Post-Licensure Safety Profile of a Prophylactic Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine, 29 Pediatric Infectious Disease Journal. 95-101 (2010); Barbara A. Slade, et al., Postlicensure Safety Surveillance for Quadrivalent Human Papillomavirus Recombinant Vaccine, 302 The Journal of the American Medical Association. 750-57 (2009).

[15] VAERS ("Vaccine Adverse Events Reporting System") is a database created, pursuant to the Vaccine Act, by the FDA and the Centers for Disease Control and Prevention to receive reports about adverse events which may be associated with vaccines. *See* Vaccine Adverse Event Reporting System, available at https://vaers.hhs.gov/about/index. *See also Nance v. Sec'y of Health & Human Servs.*, No.06-0730V, 2010 WL 3291896, at *9 (Fed. Cl. Spec. Mstr. July 30, 2010) (discussing that VAERS is a surveillance system that accepts "voluntarily submitted" reports of events from manufacturers, health care workers and patients, and the experiences reported are unsolicited and reflect a concern of a possible relationship to vaccination).

[16] Barbara A. Slade, et al., at 756-57.

For the reasons set forth above, the undersigned agrees with Respondent that the theory postulated by Petitioner concerning vaccine causation does not provide a reliable, scientific theory linking vaccination to injury under the first prong of *Althen*.

B. Althen Prongs Two and Three- A Logical Sequence of Cause and Effect and Temporal Proximity

Under the second prong of *Althen*, Petitioner is required to establish "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. The third prong of the *Althen* framework requires a petitioner to demonstrate, by a preponderance of the evidence, "a proximate temporal relationship between vaccination and injury." *Id.* Thus, if symptoms manifest later or earlier than medically expected, it is less likely that the vaccine is the cause. *See id.* Under the Vaccine Act, temporal proximity is one factor that is considered in the causation analysis, but a temporal association alone is insufficient to establish causation by a preponderance of the evidence. *See Pafford*, 451 F.3d at 1356 ("There may well be a circumstance where it is found that a vaccine *can* cause the injury at issue and where the injury was temporally proximate to the vaccination, but it is illogical to conclude that the injury was actually caused by the vaccine."); *Capizzano*, 440 F.3d at 1327.

The Federal Circuit has held that, "[there is no] reason why evidence used to satisfy one of the Althen III prongs cannot overlap to satisfy another prong." *Capizzano*, 440 F.3d at 1326. Because *Althen* prongs two and three have a closely overlapping analysis, in this case, they will both be discussed within this section. More specifically, since prong three helps to establish a connection between the causal theory of prong one and the more fact based cause and effect arguments of prong two by demonstrating, "that the onset of symptoms occurred within a timeframe from which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact," (*see, e.g., de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008); *Pafford*, 451 F.3d at 1358), the undersigned will discuss prong three first.

Petitioner received her third dose of the HPV vaccine on March 4, 2008. Pet'r's Ex. 2 at 15. Dr. Gowin puts the symptomatic onset of Petitioner's RA in the spring of 2008, (s*ee* Tr. at 10-11), and in Petitioner's affidavit, she claims joint swelling beginning in late March 2008 and June 2008. Pet'r's Ex. 15 at 1-2. However, her first documented complaint of pain that might have been RA-related was reflected in medical records from August 2008, nearly five months post-vaccination, when she sought treatment for foot pain. Pet'r's Ex. 17 at 1. While she did have long-standing complaints of hip pain, and in June complained that she could not carry a laptop due to shoulder pain, (Pet'r's Ex. 14 at 1-3), there is no indication that Petitioner's pre-existing hip and shoulder pain was arthritic in nature. Neither of the experts testified, nor did the medical records show, that Petitioner had the joint damage characteristic of RA in her hips, shoulders, or elbows at the time her RA was diagnosed. The experts also testified that large joints such as shoulders are generally the last to be affected by RA. Tr. at 36-37, 154-159. Petitioner's complaints of morning stiffness are not reported in the medical records until late September 2008, and several physicians, including a rheumatologist and an orthopedic surgeon, who examined Petitioner from June 2008 to December 2008, found no evidence of joint swelling during this period. *See* Tr. at 22-27, 124; Pet'r's Exs. 1-14, 17. Petitioner's first serology that

was weakly positive for RA was approximately eight months after vaccination, and even then, her anti-CCP antibody levels, elevation of which would have been consistent with Dr. Gowin's theory of causation, were normal. Pet'r's Ex. 8 at 10. She was not diagnosed with RA based on joint swelling and positive serology until January 20, 2009, ten months following vaccination, when her RF and anti-CCP levels indicated a somewhat mild case of RA. *Id.*; Tr. at 43. In addition, from the date of the third dose of the HPV vaccination in March 2008 to Dr. Epstein's last examination, none of Petitioner's treating physicians mentions the HPV vaccine as even a possible cause for Petitioner's RA. Tr. at 29, 140; Pet'r's Ex. 8 at 10. None of Petitioner's treating physicians, including two rheumatologists and an orthopedic surgeon, causally connected Petitioner's eventual RA diagnosis with the third dose of the HPV vaccination. *See* Pet'r's Exs. 1-14, 17.

All of these facts cast significant doubt on Dr. Gowin's assertion that "[t]he onset of [Petitioner's] disease was several weeks after her HPV vaccination series." Pet'r's Ex. 18 at 3. Rather, these facts support Dr. Lightfoot's observation that "it remains unclear precisely when trauma-related or fibromyalgia pain gave way to RA. Serologic evidence for the latter was present no earlier than on [November 1, 2008], eight months after the third HPV [injection] (and indeed was negative at four months after that injection)." Resp't's Ex. A at 6. The Stanley article, (Court Exhibit 2 at 4), shows that the peak antibody response after the third dose of an HPV vaccine is at about one month, and it is robust. Tr. at 60-62. If those robust antibodies turned against Petitioner's system via molecular mimicry, as Dr. Gowin postulates, her systemic response should also have been robust,[17] and in approximate temporal sync with the peak antibody development, that is, 4 to 8 weeks post-vaccination. Thus, even if Petitioner's theory of causation were valid, neither the very delayed, nor the relatively mild and gradual, onset of Petitioner's disease, fits with that theory. *See de Bazan*, 539 F.3d at 1352.

Based on the foregoing analysis, the undersigned concludes that Petitioner's claim fails under prong three of *Althen*, because the lapse of time between Petitioner's third dose of the HPV vaccination, in relation to the date of onset, extends well beyond the peak antibody response time as substantiated by the medical literature filed in this case. In light of this lack of a proximate temporal relationship between vaccine and injury, the undersigned also cannot find that there is "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278.

[17] The reactivity of RA sera to anti-citrullinated $E2_{345-362}$ antibodies was "significantly higher" than that documented in either sera of patients with other rheumatic diseases or sera of healthy control patients. J. Shi, et al., at 133; *see also* Pet'r's Ex. 18 at 2, "[t]hese patients had worse disease activity as well."

VI

CONCLUSION

In sum, the weight of the scientific and clinical evidence set forth by Petitioner does not support Petitioner's assertion that the HPV vaccination was the cause-in-fact of Petitioner's RA. Even if the theory set forth by Petitioner satisfied the first prong of the *Althen* test, Petitioner failed to satisfy the second prong of the *Althen* test, that this vaccination *did* cause Petitioner's injury, and the temporal relationship between vaccine and injury is simply too attenuated to satisfy the third prong of the *Althen* test. To be entitled to compensation under the Program, Petitioner must satisfy all three prongs of *Althen*. Petitioner has not done so in this case.

The undersigned is sympathetic to the fact that Petitioner suffers from RA. However, under the law, the undersigned can authorize compensation only if a medical condition or injury either falls within one of the "Table Injury" categories, or is shown by medical records or a competent medical opinion to be vaccine-caused. No such proof exists in the record. Therefore, the undersigned has no choice but to hereby DENY this claim. The Clerk shall enter judgment in accord with this decision.

IT IS SO ORDERED.

/s/ Lisa D. Hamilton-Fieldman
Lisa D. Hamilton-Fieldman
Special Master